Available online at www.sciencedirect.com
ScienceDirect
Biochimica et Biophysica Acta 1773 (2007) 1311 – 1340
Biochimica et Biophysica Acta
BBA
www.elsevier.com/locate/bbamcr

Review

Function and regulation in MAPK signaling pathways: Lessons learned from the yeast *Saccharomyces cerevisiae*

Raymond E. Chen, Jeremy Thorner *

Division of Biochemistry and Molecular Biology, Department of Molecular and Cell Biology, University of California, Berkeley, CA 94720-3202, USA

Received 19 February 2007; received in revised form 2 May 2007; accepted 4 May 2007
Available online 22 May 2007

Abstract

Signaling pathways that activate different mitogen-activated protein kinases (MAPKs) elicit many of the responses that are evoked in cells by changes in certain environmental conditions and upon exposure to a variety of hormonal and other stimuli. These pathways were first elucidated in the unicellular eukaryote *Saccharomyces cerevisiae* (budding yeast). Studies of MAPK pathways in this organism continue to be especially informative in revealing the molecular mechanisms by which MAPK cascades operate, propagate signals, modulate cellular processes, and are controlled by regulatory factors both internal to and external to the pathways. Here we highlight recent advances and new insights about MAPK-based signaling that have been made through studies in yeast, which provide lessons directly applicable to, and that enhance our understanding of, MAPK-mediated signaling in mammalian cells.

Keywords: Mitogen_activated protein kinase; MAPK; Fus3; Kss1; Hog1; Mpk1/Slt2; Smk1; Mitogen_activated protein kinase kinase; MAPKK; Ste7; Pbs2; Mkk1; Mkk2; Mitogen_activated protein kinase kinase kinase; MAPKKK; Ste11; Ssk2; Ssk22; Bck1; Mitogen_activated protein kinase kinase kinase kinase; MAPKKKK; Pkc1; p21_activated protein kinase; PAK; Ste20; 5′_AMP_activated protein kinase; AMPK; Snf1; 3′,5′_cyclic AMP_dependent protein kinase; PKA; Tpk1; Tpk2; Tpk3; Pheromone response; Filamentous growth response; Hyperosmotic stress response; Cell wall integrity; Signaling; Meiosis and sporulation; Signal transduction mechanisms; Signal propagation; Signaling fidelity; Spatial and temporal regulation; Yeast; Saccharomyces cerevisiae; Baker's yeast; Budding yeast

1. Introduction

A fundamental property of living cells is the ability to sense and respond appropriately to changing environmental conditions and various other stimuli. One frequently utilized molecular device for eliciting these responses is the three-tiered cascade of protein kinases known as the mitogen-activated protein kinase (MAPK) module [1]. Our current understanding of MAPK pathways is based in large part on research that was conducted first in the eukaryotic microbe, *Saccharomyces cerevisiae* (also known as baker's yeast or budding yeast). Many of the components of these pathways and the mechanisms by which they operate were first identified and characterized in this organism and are now known to have been conserved during the evolution of the entire eukaryotic kingdom. This yeast has served its pathfinding role because it is highly amenable to genetic, biochemical, and cell biological studies, and was the first eukaryote to have its entire genome sequenced.

In this article, we begin with an overview of the MAPK pathways in *S. cerevisiae* and the mechanisms of their activation in response to signals or stresses. We then discuss the mechanisms by which these pathways regulate downstream molecular and cellular processes. We also consider the mechanisms by which these pathways are themselves regulated by components both internal and external to the core signal transduction machinery of each pathway. Throughout, our emphasis is on new insights that have been gleaned from studies during the last few years and, importantly, on how the molecular mechanisms and general principles unveiled by these recent studies continue to illuminate previously unappreciated features of MAPK signaling that are more difficult to discern in more complex organisms.

* Corresponding author. Department of Molecular and Cell Biology, University of California, Room 16, Barker Hall, Berkeley, CA 94720-3202, USA. Tel.: +1 510 642 2558; -3574 (secr.); fax: +1 510 642 6420.
E-mail address: jthorner@berkeley.edu (J. Thorner).

0167-4889/$ - see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbamcr.2007.05.003

2. Core activation modules

2.1. MAPK cascades

The canonical MAPK pathway contains a key, three-component signal relay in which an activated MAPK kinase kinase (MAPKKK or MEKK) activates a MAPK kinase (MAPKK or MEK), which then activates a MAPK (or ERK, for extracellular signal-regulated kinase) (Fig. 1). MAPKKKs contain an N-terminal regulatory domain and a C-terminal serine/threonine protein kinase domain. Upon activation, a MAPKKK phosphorylates two serine or threonine residues at conserved positions in the activation loop of its target MAPKK, which is a dual-specificity (serine/threonine and tyrosine) protein kinase. The activated MAPKK then proceeds to phosphorylate both the threonine and tyrosine residues of a conserved –Thr–X–Tyr– motif in the activation loop of its target MAPK. These phosphorylations activate the MAPK by causing substantial conformational changes, and point mutations in which these phosphoacceptor residues are changed to acidic residues (Glu or Asp) do not suffice to activate MAPKs. In contrast, such phosphomimetic mutations are frequently able to confer constitutive activity to other sub-classes of protein kinases, including MAPKKs. MAPKs are serine/threonine protein kinases in the same CMGC group as cyclin-dependent kinases (CDKs) and phosphorylate their substrates at –Ser/Thr–Pro– motifs.

To initiate a MAPK cascade, the MAPKKK must be activated. Upstream events that can lead to MAPKKK activation include processes such as occupancy of receptors coupled to heterotrimeric G proteins by their cognate agonists and the binding of the appropriate ligands to other classes of receptors that stimulate production of activated monomeric G-proteins, or both. In contrast to MAPKKKs and MAPKKs, for which a paucity of physiologically relevant substrates have been described (other than their MAPKK and MAPK targets, respectively), MAPKs phosphorylate a diverse set of well-characterized substrates, including transcription factors, translational regulators, MAPK-activated protein kinases (MAPKAP kinases), phosphatases, and other classes of proteins, thereby regulating metabolism, cellular morphology, cell cycle progression, and gene expression in response to a variety of extracellular stresses and molecular signals.

2.2. The Cdc42-PAK module: G-proteins, protein kinases, and adaptors

Three of the MAPK pathways present in yeast are activated by a common agent, namely, a member of the p21-activated protein kinase (PAK) family of protein kinases, Ste20 (Fig. 1). In this case, the p21 is the small, monomeric Ras-related GTPase, Cdc42. Ste20 is activated by Cdc42 as follows: the C-terminal kinase domain of Ste20 is held in an inactive state by association with an autoinhibitory sequence present in its N-terminal domain that overlaps with a Cdc42/Rac interactive binding (CRIB) motif; binding of active (GTP-bound) Cdc42 to the CRIB motif relieves this autoinhibition [2]. In all three pathways, activated Ste20 is responsible for phosphorylating and activating Ste11, and thus serves as a MAPKKK kinase (MAPKKKK) [3,4]. Hence, in each pathway, upstream events

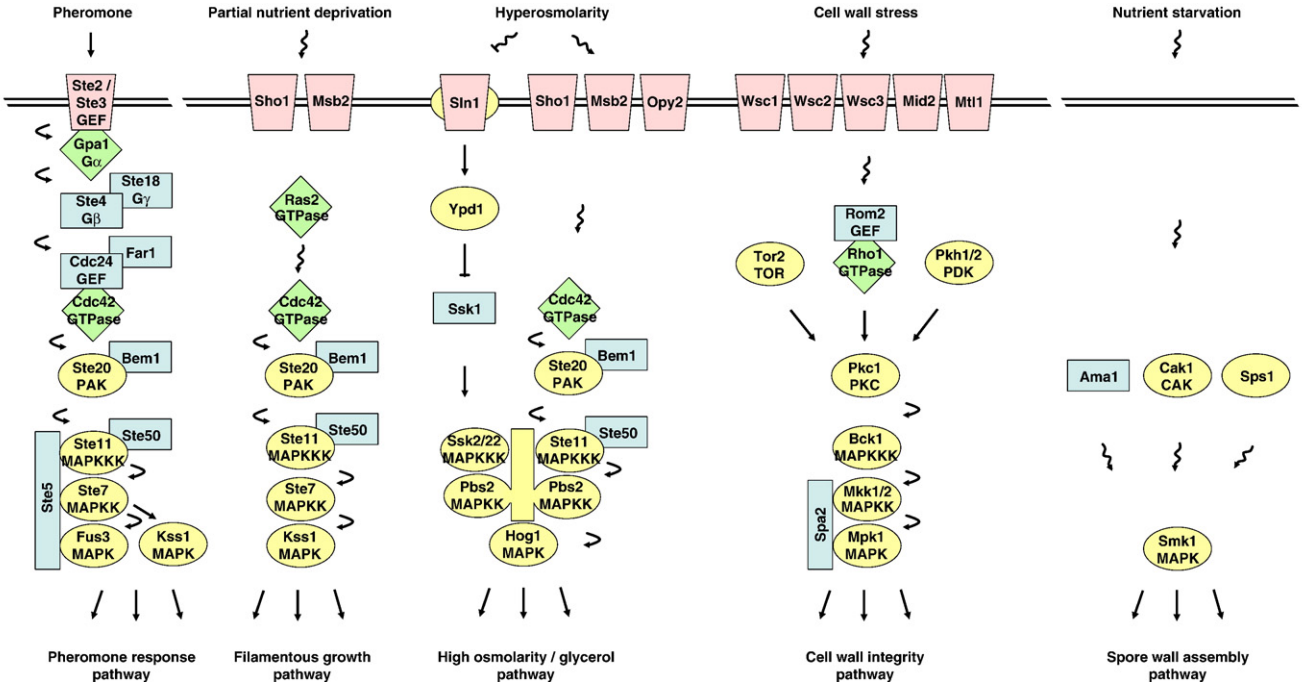

Fig. 1. Schematic diagrams of the MAPK signaling pathways in *S. cerevisiae*. Symbols are: protein kinases, ovals; GTP-binding proteins, diamonds; scaffold, adaptor, and activating proteins, rectangles; cell surface proteins, trapezoids; activation, arrows; inhibition, T-bars; direct action, smooth lines; indirect action (or unknown molecular mechanism), squiggly lines. For clarity, not all factors and interactions are shown, connections to other pathways and processes upstream of the MAPKs are omitted, and direct targets of the MAPKs are not included (see the text for these details).